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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/995,847	11/28/2001	Carlo Dante Rizzuto	ENGE-P01-004	3197

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,847	RIZZUTO ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,13,14,18-24,26-30,32,33 and 36-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 13, 14, 18-24, 26-30, 32, 33, 36-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 19 January 2006 in response to the Final Office Action mailed 7 September 2004. Claims 2, 7, 8 and 10-45 were considered in the 7 September Office Action. Claims 7, 8, 10-12, 15-17, 21, 22, 25, 34 and 35 were canceled and claims 2, 13, 14, 18, 20, 24, 26, 27-30, 32, 33 and 36-40 were amended in the 19 January Paper. Claims 2, 13, 14, 18-24, 26-30, 32, 33 and 36-45 are pending and under consideration.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 January 2006 has been entered.

Response to Amendment and Arguments

Rejection of claims 7, 8, 10-12, 15-17, 21, 22, 25, 34 and 35 is rendered moot by cancellation of the claims.

Claim Rejections - 35 USC § 112, possession

Claims 2, 13, 14, 18-24, 26-30, 32, 33 and 36-45 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record and herein below in the response to arguments.

The Office Action mailed 19 December 2003 concludes that the skilled artisan would not have viewed the teachings of the specification as sufficient to show that Applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of any molecule having the function of a molecular clasp. The rejection was made for the reasons set forth at pages 4-9 of the 19 December Office Action and maintained for reasons set forth in the 7 September Office Action at pages 4-12.

Response to Arguments

In response to the *prima facie* case and arguments of record, Applicant has amended the claims such that the molecular clasp is limited to comprising the general architecture of (N)-fluorophore effector1-single chain antibody domain 1 (scFv1)-transducer-scFV2-fluorophore effector2-(c), wherein scFv1 and scFv2 together form the molecular recognition element (MRE) wherein in response to ligand binding to said MRE, fluorophore effector1 and effector2 are juxtaposed to produce a detectable fluorescent change.

In the remarks, Applicant contends that the nature of the allosteric property required to provide the recited function (*i.e.*, in response to ligand binding to said MRE, fluorophore effector1 and effector2 are juxtaposed to produce a detectable fluorescent change) is relatively

straightforward and rather predictable, partly, because scFv has well-characterized structure. Applicant cites a statement in the paragraph bridging pages 21-22 of the specification which is quoted in the remarks as follows:

> [I]n the ligand free state,...portions of the single chain antibody domain distal from the ligand binding site are physically separated. Ligand binding drives the ligand binding site into its preferred, 'natural' conformation such that the distal ends of the single chain antibody domains are juxtaposed.

Applicant further cites Figures 1, 5 and 6 and provides a diagram in the remarks that is purported to illustrate the configuration contemplated in the specification. Based on this interpretation of the specification, Applicant asserts on page 8 of the remarks that the maximum distance between the two effectors is much larger in the ligand-free state than in the ligand bound state and when there is no ligand binding, the transducer linking the two scFv's may only be loosely associated with each other, if at all. Applicant urges, "It should be noted that the transducer in the claimed invention need not contribute to the conformation change. It may simply 'permit' the two scFv's to come together to form a ligand binding pocket."

These arguments have been fully considered but are not deemed persuasive. The portion of the statement quoted by Applicant reads, in full:

> [I]n the ligand free state, the transducer 20 contorts the ligand binding site such that portions of the single chain antibody domain distal from the ligand binding site are physically separated. Ligand binding drives the ligand binding site into its preferred, 'natural' conformation such that the distal ends of the single chain antibody domains are juxtaposed.

Thus, Applicant has omitted the portion of the statement which describes the function of the transducer in the particular configuration being described, which is to actually contort the molecule such that the portions distal to the ligand binding site are physically separated while the ligand binding site itself remains intact. The teaching, "Ligand binding drives the ligand binding site into its preferred, 'natural' conformation such that the distal ends of the single chain antibody domains are juxtaposed", coupled with the teaching omitted by Applicant, clearly indicates that the 'natural' conformation of the single chain antibody, *i.e.*, absent of contortion of the ligand binding site by the transducer, is with the distal ends of the single chain antibody domains juxtaposed. This is in contrast to the model presented on page 7 of Applicant's remarks, wherein the function of the transducer appears merely to be a tether preventing the two domains of the single chain antibody from diffusing away from each other. Clearly, this is not what is being taught in the statement cited by Applicant.

Furthermore, the computer modeling described in Example 1 is based on the transducer disrupting or torquing the natural V_H-V_L interface of the single chain antibody comprised by the molecular clasp such that the distance between the YFP and CFP in the absence and presence of ligand is sufficiently different that a difference in fluorescence transfer is detectable. Thus, the simple model suggested in Applicant's remarks is not consistent with the models presented in the specification and is based on an incomplete quotation of the cited teaching. Clearly, in the invention contemplated in the specification, the transducer must sufficiently alter the natural structure of the single chain antibody molecule as a whole such that the distal ends of the molecule are forced apart while the structure of the ligand binding domain remains sufficiently intact such that the binding domain still recognizes ligand, and ligand binding "drives the ligand

binding site into its preferred, 'natural' conformation". In addition, the molecule as a whole must be configured such that ligand binding to the binding site induces a conformational change of sufficient magnitude to produce a measurable change in fluorescence energy transfer between the two fluorescent effector molecules. Still further, the effectors of the claims can be any fluorophore, each of which would have unique fluorescence properties, and the degree of allosteric change required to obtain a detectable fluorescent change would be distinct for each combination of fluorescent proteins. See *e.g.*, page 16, lines 19-22 of the specification, which states, "The characteristic distance R_0 at which FRET is 50% efficient depends on the quantum yield of the donor moiety (i.e., the shorter-wavelength fluorophore), the extinction coefficient of the acceptor moiety (i.e., the longer-wavelength fluorophore), and the overlap between the emission spectrum of the donor moiety and the excitation spectrum of the acceptor moiety" and page 19, lines 24-25, which states, "The nature of the MRE, ligand, and transducer each affect FRET and the response of the indicator to analyte" (page 19, lines 24-25). These teachings are clearly not consistent with the simple model and statements found in Applicant's remarks. Thus, a description of a single species of molecular clasp comprising a single chain antibody comprising a given MRE, a given transducer molecule and a given pair of fluorescent proteins configured such that ligand binding to the MRE provides a detectable fluorescence signal is not representative of a broad genus of any combination of single chain antibody/MRE, transducer and fluorescent effectors so configured.

In the fourth paragraph on page 8 of the remarks, Applicant asserts that the sequence variations among different scFv's is "pretty conserved" and the major differences probably reside in the three Ag-recognizing CDR regions of each scFv domain, which are merely a few

amino acids long each. Applicant contends, based on this, that different scFv's, even having different ligand specificity, will predictably produce substantially the same conformational change.

This argument has been fully considered but is not deemed persuasive. As described above, the teachings of the specification indicate that the nature of the MRE, ligand, and transducer each affect FRET (*Id.*). Thus, the allosteric change resulting from the binding of any given ligand to any given scFv MRE, wherein the natural structure of the scFv is modified by any given transducer, is determined by the particular properties of the MRE (i.e., the variable Ag-recognizing CDR regions of each scFv domain), the properties of the ligand and the specific properties of the transducer. Furthermore, as obtaining a detectable fluorescent change from any given fluorescence pair would require a distinct allosteric change in the molecule depending on the quantum yield of the donor moiety, the extinction coefficient of the acceptor moiety, and the overlap between the emission spectrum of the donor moiety and the excitation spectrum of the acceptor moiety, a description of a given combination of scFv MRE, transducer operative with any given fluorescence pair does not describe the broad scope of any ScFv MRE coupled to any given transducer and any given fluorophore effector configured such that ligand binding to the MRE results in juxtaposition of the fluorophores to produce a detectable fluorescent change. In view of these considerations, the skilled artisan would not recognize the prophetic teachings of the specification as demonstrating that Applicant was in possession of the broad scope of what is presently claimed at the time the application was filed.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph as lacking adequate written description.

Claim Rejections - 35 USC § 112, enablement

Claims 2, 13, 14, 18-24, 26-30, 32, 33 and 36-45 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modular molecular clasp comprising a single chain antibody 1LMK or 1A14 comprising YFP and CFP effector molecules, does not reasonably provide enablement for the broad scope of any molecular clasp comprising two single chain antibody domains together forming a molecular recognition element comprising a ligand binding site; any effector and any transducer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims for reasons set set forth in the 19 December Office Action at pages 9-14 and in the 7 September Office Action at pages 12-17.

Response to Arguments

In response to the *prima facie* rejection and arguments of record, Applicant has amended the claims as described herein above and contends that, in view of the well-conserved three-dimensional folding of scFv, the skilled artisan would be able to make and use the invention without undue experimentation.

This argument is not deemed persuasive because, as described above, the teachings of the specification indicate that the nature of the MRE, ligand, and transducer each affect FRET (*Id.*).

Thus, the allosteric change resulting from the binding of any given ligand to any given scFv MRE, wherein the natural structure of the scFv is modified by any given transducer, is determined by the particular properties of the MRE (i.e., the variable Ag-recognizing CDR regions of each scFv domain), the properties of the ligand and the specific properties of the transducer. Furthermore, according to the teachings of the specification, obtaining a detectable fluorescent change from any given fluorescence pair would require a distinct allosteric change in the molecule depending on the quantum yield of the donor moiety, the extinction coefficient of the acceptor moiety, and the overlap between the emission spectrum of the donor moiety and the excitation spectrum of the acceptor moiety (See *supra*). Given these teachings and the unpredictable nature of the art established in previous Office Actions, the skilled artisan would not be able to make the full scope of the claimed without undue experimentation.

In response to the Examiner's contention that the combined resources of a pharmaceutical company or the biomedical community is well above what is ordinary and what might be routine for a pharmaceutical company would not be routine for one of ordinary skill, Applicant argues that the factors determining the level of skill in the art do not relate to the facility in which the skilled artisan works or the type/amount of resources he has access to.

Applicant's arguments misrepresent the Examiner's position. The statement referred to by Applicant was made by the Examiner specifically in response to Applicant's statement, "Applicants submit that the amount of experimentation involved in constructing a library of randomly mutagenized candicate [sic] molecules for screening, and the actual screening itself is not overly large in view of the relative level of skill in the art (which is high) at the time of filing. In fact, pharmaceutical companies routinely screen billions of molecules, if not more, in

identifying potential drug molecules" (page 17 of the Paper filed 23 June 2004; emphasis added). By this statement, Applicant appeared to be insinuating that it would be routine for one of ordinary skill in the art to screen billions of molecules, if not more, to identify a functional molecular clasp because it would be routine for a pharmaceutical company, as a whole, to screen billions of molecules. If this is not what was intended by the assertion that it is routine for pharmaceutical companies to screen billions of molecules to identify potential drug molecules, Applicant is urged to clarify the relevance of large scale screening of compounds by pharmaceutical companies to the amount of experimentation required for one of ordinary skill in the art to make what is presently claimed.

Next, Applicant acknowledges that the art cited to support the *prima facie* case teaches that each biosensor is unique and requires substantial development time but contends that the claimed molecular clasp contains unique designs using specific types of effectors and MREs and the art does not *per se* contradict the enablement of the claimed invention. In particular, Applicant contends that the scFv technology is mature and has been routinely used at the time of filing of the application. Applicant urges that numerous studies have confirmed that the binding affinity by scFv approximates that of the original monoclonal.

This argument has been fully considered but is not found persuasive. The art cited in the *prima facie* rejection establishes the underdeveloped state of the art relevant to the construction of biosensors and, coupled with the teachings of Richards (also cited in the discussion of the art at pages 11-12 of the 19 December Office Action), which establishes that even small changes in protein structure can have dramatic effects on function, demonstrate the unpredictable nature of the relevant art. Applicant's assertion that the scFv art was mature and routinely practiced at the

time of filing is not persuasive because the claims are not directed to an scFv. Instead, the claims are directed to a molecular clasp that comprises scFv domains as a component part. As Applicant points out, the art does not teach a biosensor having the characteristics recited in the instant claims. In fact, neither the disclosure nor the relevant art, five years after the application was filed, disclose a working molecular clasp comprised of single chain antibody domains and fluorophores. Instead, as pointed out in previous Office Actions, the disclosure provides only prophetic assertions that such molecules can be made based on modeling of a single species within the scope of the claims. Even if one accepts, *arguendo*, that the art of single chain antibodies is mature and predictable, in light of the generally unpredictable nature of biosensors and protein engineering and the absence of a single working example of what is presently claimed, the skilled artisan clearly would not view construction of molecular clasp polypeptides having the characteristics recited in the claims as routine. In other words, the skilled artisan in an unpredictable art would not view making something that has never been made as routine.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking an enabling disclosure.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action

after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER